REMARKS / ARGUMENTS

Status of the Claims

Claims 1-22 are pending, have been examined in the present application and stand rejected under 35 U.S.C. §103. Applicants hereby amend claims 1 and 18. After entry of this paper claims 1-22 remain pending for examination.

Amendments to the Claims

Claim 1 has been amended to clarify that the step of electrophoresing separates two or proteins in the mixture. Support for the amendments to claim 1 are found in original claim 1 and the throughout the specification and thus, add no new matter. Claim 18 has been amended to correct an inadvertent typographical error; and accordingly, adds no new matter.

Rejections Under 35 U.S.C. 103

Claims 1-3, 6-9 and 10-21 have been rejected under 35 U.S.C. §103 as allegedly obvious over International Patent Application Publication No. WO 00/11208 by Aebersold et al. ("Aebersold") in view of Bienvenut et al. (Analytical Chem., 1999, vol. 71, pp. 4800-4807) ("Bienvenut"). Claims 1-8 and 10-21 have been rejected as allegedly obvious over Aebersold in view of Gygi et al. (Nature Biotechnology, 10/1999, vol. 17, pp. 994-999) ("Gygi")

Dependent claims 4 and 5 have been rejected as allegedly obvious over Aebersold in view of Bienvenut and U.S. Patent No. 5,538,897 to Yates et al. ("Yates"); claim 9 as allegedly obvious over Aebersold in view of Gygi and Bienvenut; and claim 22 as allegedly obvious over Aebersold in view of Bienvenut and Clauser et al. (Proceeding of the National Academy of Science, USA, 1995, 92(11), pp. 5072-6) ("Clauser").

Applicants respectfully submit that Aebersold, Bienvenut, Gygi, Yates, and Clauser (collectively "the cited references"), either alone or in proper combination, do not render Applicants' claims obvious because one of ordinary skill in the art would neither have been motivated to combine the cited references nor have had a reasonable expectation of successfully combining these references to produce Applicants' claim 1 as a whole.

First, none of the cited references suggest combining an affinity labeling step with both a step that separates labeled proteins by electrophoresis and a step that detects labeled peptides by mass spectrometry as set forth in Applicants' claim 1. Indeed, the cited references never mention subjecting affinity labeled proteins to electrophoresis to separate proteins.

Second, Applicants respectfully submit that this failure of the cited references to suggest the combination is not surprising as one of ordinary skill in the art would not have had a reasonable expectation of successfully separating labeled proteins by electrophoresis as set forth in Applicants' claims when using the labeling technique described by Aebersold.

Specifically, one of ordinary skill in the art would not have reasonably expected that proteins labeled with an affinity label as described in Aebersold to be separated in a useful manner by electrophoresis because the chemistry involved in this labeling can change both the confirmation and molecular weight of the labeled proteins in an unpredictable manner. As a result, one of ordinary skill in the art would have expected that proteins labeled according to Aebersold would not separate by electrophoresis in a reproducible or useful manner. Accordingly, one of ordinary skill in the art would have expected that combining the affinity labeling of Aebersold with an electrophoresis technique (e.g., a gel electrophoresis technique) would render the electrophoresis technique unsuitable for its intended purpose, e.g., separation of proteins on the basis of molecular weight (MW).

In particular, there are at least two aspects to the chemistry of the affinity labeling technique described in Aebersold that would have led one of ordinary skill in the art to reasonably conclude that such labeled proteins would not separate by electrophoresis in either a reproducible or useful manner. The first aspect relates to the number of affinity labels that would bind to a protein. A typical protein contains multiple sites to which an affinity label of Aebersold could bind. For example, albumin (a common blood protein) contains 35 cysteine groups. One of ordinary skill in the art would reasonably predict that if a sample of albumin was affinity labeled according to the teachings of Aebersold, that instead of each protein receiving the same number of labels, there would be a distribution of the number of labels per protein. For example, some albumin proteins would receive 10 labels, some 20 labels, some 35 labels and maybe even some would have as few as one label. As each affinity label adds mass to the protein (i.e., increases the MW of the labeled entity), the result of such a distribution of labels

would be to smear out the electrophoretic band corresponding to the protein. As a result, one of ordinary skill in the art would not reasonably expect to separate such labeled proteins in a reliable or useful manner by electrophoresis. In addition, this distribution, for the same protein, could vary from experiment to experiment leading to irreproducible results. Accordingly, one of ordinary skill in the art would not have had a reasonable expectation of successfully combining the affinity labeling of Aebersold with electrophoresis separation to practice one or more of Applicants' claims because she would have expected such labels to render the electrophoresis step inoperable for its intended purpose.

The second aspect of the chemistry relates to the confirmational changes one of ordinary skill in the art would anticipate occurring for proteins affinity labeled as described in Aebersold. Specifically, one of ordinary skill in the art would understand that the affinity labeling conditions described in Aebersold denature the proteins so labeled. As a result, the ordinary artisan would have predicted that the affinity labels of Aebersold change the confirmation of the proteins so labeled and that a distribution of confirmations would occur. As each confirmation can have a different migration rate during electrophoresis, the ordinary artisan would have reasonably predicted that these changes in confirmation would further smear out the electrophoretic band corresponding to the protein in addition to the smearing already predicted due to a distribution in the number of labels per protein. Accordingly, one of ordinary skill in the art would not have had a reasonable expectation of successfully combining the affinity labeling of Aebersold with electrophoresis separation to practice one or more of Applicants' claims because she would have reasonably expected such labels to render the electrophoresis step inoperable for its intended purpose by smearing out the electrophoretic band such that no meaningful separation could be achieved.

Applicants therefore respectfully submit that the cited references, either alone or in proper combination, cannot be combined to produce claim 1 as a whole because: (a) none of the cited references or the art teach or suggest such a combination; and (b) one of ordinary skill in the art would not have had a reasonable expectation of successfully combining the affinity labeling of Aebersold with electrophoresis separation to produce claim 1 as a whole. Accordingly, Applicants submit that claim 1, and claims 2-22 that depend therefrom, are novel and non-obvious over the cited references.

CONCLUSION

In view of the above, it is believed that all presently pending claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone call would serve to clarify issues or expedite the prosecution of this case, the Examiner is invited to call the undersigned at (508) 383-7406.

Applicant believes no additional fee, beyond the fee for a Petition for a two-month extension, is due with this Request for Continued Examination. However, if any additional fee is due, please charge our Deposit Account No. 50-1191, under Order No. SYP-172, from which the undersigned is authorized to draw.

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Respectfully submitted,

By Andrew T. Karnakis

Andrew T. Karnakis, Esq.
Registration No.: 27,909
Applied Biosystems
500 Old Connecticut Path
Framingham, Massachusetts 01701
(508) 383-7406
Attorney For Applicant